BAYER AG *WO 200270484-A1

2001.03.05 2001-1010438(+2001DE-1010438) *(2002.09.12)* C07D 213/85, A61K 31/4418, 31/443, C07D 405/04, 417/12, 409/12, A61K 31/4436, A61P 9/00

**Adenosine receptor-specific ligand medicaments, comprising new or known 6-amino-4-phenyl-2-oxy-pyridine-3,5-dicarbonitrile derivatives, useful e.g. for treating cardiovascular diseases, cancer, inflammation, pain or diabetes (Ger)**

C2002-195540 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW)

Addnl. Data: ROSENTRETER U, KRAEMER T, VAUPEL A, HUEBSCH W, DIEDRICHS N, KRAHN T, DEMBOWSKY K, STASCH J

2002.02.20 2002WO-EP01758

B(6-H, 7-D4B, 14-C1, 14-C3, 14-D2, 14-F1, 14-F2, 14-F4, 14-F7, 14-H1, 14-J1A3, 14-J1A4, 14-K1, 14-N7, 14-N12, 14-N16, 14-N17, 14-P2, 14-S4) .11

NOVELTY

The use of 6-amino-4-phenyl-2-oxy-pyridine-3,5-dicarbonitrile derivatives (I) for the prophylaxis and/or treatment of diseases is new. Compounds (I) are new, with some specific exclusions.

DETAILED DESCRIPTION

Pyridine derivatives of formula (I) and their salts, hydrates, hydrated salts and solvates are claimed for the prophylaxis and/or treatment of diseases.

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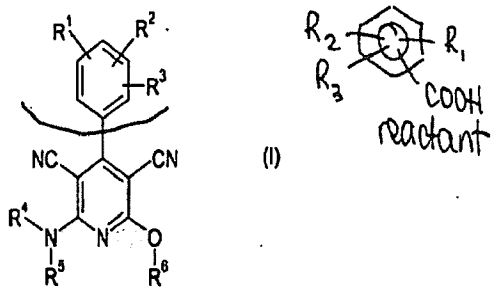


$R_1$ - $R_3$ = alkyl (optionally substituted (os) by 1-3 of OH, OT, cycloalkyl, alkenyl, alkynyl, halo or aryloxy); aryl (os by 1-3 of halo, $NO_2$, OT, COOH, COOT, NHT or $NT_2$); alkoxy (os by 1-3 of OH, OT, 3-6C cycloalkyl, alkenyl, alkynyl, aryl, Het, aryloxy, halo, CN, COOT, $NH_2$, NHT or $NT_2$); or H, OH, halo, $NO_2$, CN or $-NHCOR_7$;

or $R_1 + R_2$ (on adjacent C) = group completing a 5-7 membered saturated or partially unsaturated heterocycle containing 1 or 2 of N, O and/or S as heteroatom(s) (os by T or =O);

T = 1-4C alkyl;

Het = 5-10 membered heteroaryl containing 1-3 of N, O and/or S as heteroatom(s);

$R_7$ = alkyl (os by OH or OT), cycloalkyl or aryl (os as in $R_1$);

$R_4$, $R_5$ = H, alkyl (os by OH, OT, cycloalkyl, aryl or Het') or 3-8C cycloalkyl (os by OH or alkyl);

or $NR_4R_5$ = 5-7 membered saturated or partially unsaturated heterocycle (optionally containing 1 or 2 of N, O and/or S as further heteroatom(s) and os by 1-3 of =O, F, Cl, OH, 1-6C alkyl or 1-6C alkoxy);

Het' = 5- or 6-membered heteroaryl containing 1-3 of N, O and/or S as heteroatom(s);

$R_6$ = cycloalkyl or alkyl (os by cycloalkyl, OH, OT, alkenyl, alkynyl, aryl or Het, aryl and Het themselves being os by halo, T, OT, $NH_2$, NHT, $NT_2$, $NO_2$, CN or OH);

unless specified otherwise alkyl moieties have 1-8C, alkenyl or alkynyl moieties 2-4C, cycloalkyl moieties 3-7C and aryl moieties 6-10C.

INDEPENDENT CLAIMS are included for:

(i) (I) (including salts etc.) as new compounds, with the exception of (I; $R_1$ - $R_5$ = H; $R_6$ = Me, Et, propyl or isopropyl), (I; $R_1$ = 4-Me, 4-OMe, 2-Cl, 4-Cl, 3-Me or 2-OH; $R_2$ - $R_5$ = H; $R_6$ = Et), (I; $R_1$ = 4-F

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or 4-OMe: $R_2$ - $R_5$ = H; $R_6$ = Me) or (I; $R_1 + R_2 = OCH_2O$; $R_3$ - $R_5$ = H; $R_6$ = Me); and

(ii) the preparation of the new compounds (I).

ACTIVITY

Cardiant; vasotropic; hypotensive; antiarteriosclerotic; antianginal; thrombolytic; anticoagulant; cerebroprotective; uropathic; cytostatic; antiinflammatory; antiasthmatic; dermatological; neuroprotective; nootropic; antiparkinsonian; analgesic; hepatotropic; antidiabetic; vulnerary.

MECHANISM OF ACTION

Adenosine receptor-specific ligand. (I) are in general selective ligands for adenosine-A1, -A2a and/or -A2b receptors; in particular (I; $R_1 + R_2 = OCH_2O$, $OCH_2CH_2O$ or $O(CH_2)_3O$) are selective for A1 receptors and (I: one of $R_1$ - $R_3$ = $NHCOR_7$; one of $R_4$ and $R_5$ = benzyl or pyridylmethyl) are selective for A1 and/or A2b receptors. The ligands may be agonists or antagonists.

USE

(I) are especially used for the treatment and/or prophylaxis of cardiovascular diseases, urogenital diseases, cancer, inflammatory or neuroinflammatory diseases, pain, respiratory tract diseases, liver fibrosis, liver cirrhosis or diabetes (all claimed). Specific disorders to be controlled include coronary heart disease, hypertension, restenosis, arteriosclerosis, tachycardia, arrhythmia, stable or unstable angina pectoris, atrial flutter, thromboembolic disease, myocardial infarction, cerebral stroke, transitory ischemic attacks, bladder irritation, erectile dysfunction, female sexual dysfunction, asthma, inflammatory dermatosis, Alzheimer's disease, Parkinson's disease, chronic bronchitis, pulmonary emphysema, bronchiectasis, cystic fibrosis, pulmonary hypertension, diabetes mellitus or wound healing deficiency.

ADVANTAGE

(I) have higher selectivity for particular adenosine receptor subtypes than prior art compounds

SPECIFIC COMPOUNDS

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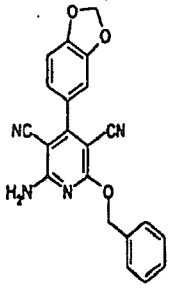
(con 4)

20 Compounds (I) are disclosed, e.g. 2-amino-4-(1,3-benzodioxol-5-yl)-6-benzyloxy-pyridine-3,5-dicarbonitrile (Ia).



(Ia)

ADMINISTRATION

Dosage is 0.1-10000 (preferably 1-100) µg/kg parenterally or 0.1-10 (preferably 1-4) mg/kg orally. (I) may also be administered locally.

EXAMPLE

A solution of 344 mg sodium in 20.7 ml benzyl alcohol was treated with 660 mg malonodinitrile and 750 mg piperonal, stirred for 16 hours at room temperature, neutralized and partitioned between water and dichloromethane. The organic phase was worked up to give, after chromatographic purification, 872 mg (40.1%) of 2-amino-4-(1,3-benzodioxol-5-yl)-6-benzyloxy-pyridine-3,5-dicarbonitrile (Ia).

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: Three methods of preparation of (I) are claimed. Typically (a) a pyridine derivative of formula (II) is reacted with an amine of formula $NHR_4R_5$ (III); or (b) a benzaldehyde derivative of formula (VII) is reacted with malonodinitrile and an alcohol of formula $R_6OH$ (VI) in presence of a base to give (I; $R_4$, $R_5$ = H).



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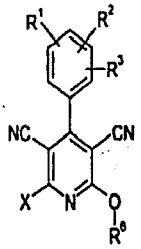
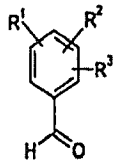


(I)



(VII)

X = leaving group.

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